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| 10/501,412 | 07/12/2004 | Amedeo De Tomassi | ITR0037YP | 6096 |

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| EXAMINER | |
|---|---|
| POPA, ILEANA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/501,412 | DE TOMASSI ET AL. | |
| | Examiner | Art Unit | |
| | Ileana Popa | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20,24 and 27* is/are pending in the application.

4a) Of the above claim(s) *6 and 15-19* is/are withdrawn from consideration.

5)☒ Claim(s) *3-5,7-11 and 14* is/are allowed.

6)☒ Claim(s) *1, 2, 12, 13, 24, and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of the invention of Group I, drawn to a GBV-B replicon comprising the GBV-B 5'-UTR, a selection or reporter sequence, an internal ribosome entry site (IRES), a NS3-NS5B sequence, and the GBV-B 3'-UTR, and of the species of bases 446-487 of SEQ ID NO: 1, in the reply filed on 02/09/2007 is acknowledged. The traversal is on the ground(s) that that the unity of invention is provided by the GBV-B replicon disclosed in claim 1 and that the Office failed to indicate where Lohman et al. describe replicon containing sequences substantially similar to the GBV-B based region provided in claim 1, wherein substantially similar sequences are defined .in the specification as having a sequence identity of at least 85% (p. 11,lines 25 and 26 of the instant specification). This is not found persuasive because, although the prior art does not disclose sequences substantially similar to those recited in claim1, the instant invention is obvious over the prior art (see the rejection under 103(a) below).

The requirement is still deemed proper and is therefore made FINAL.

Claims 21-23, 25, 26, and 28-47 have been cancelled. Claims 6 and 15-19 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and species, there being no allowable generic or linking claim.

Claims 12, 13, 24, and 27 have been amended.

Claims 1-5, 7-14, 20, 24, and 27 are under examination.

### *Claim Rejections - 35 USC § 112, 2nd paragraph*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

3. Claims 24 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: disclosing how to "cure" the cell to obtain "a cured cell".

4. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the expression vector comprising the replicon. It is noted that the replicon *per se* cannot be used to transfect cells. The replicon must be within an expression vector, wherein the expression vector is used to transfect the cells.

### *Claim Rejections - 35 USC § 112, enablement*

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 24 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of *in vitro* making a GBV-B replicon enhanced cell, does not reasonably provide enablement for a method of making a GBV-

B replicon enhanced cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

*Wands* states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

Claims 24 and 25 are directed to a method of obtaining a GBV-B replicon permissive cell. The instant specification teaches by exemplification the obtaining GBV-B replicon permissive cell *in vitro*, wherein Huh-7 permissive cells transfected with an expression vector encoding GBV-B replicons are treated with IFN-α to eliminate the replicon and retransfected to obtain permissive cells capable of replicating the GBV-B replicon with increased efficientcy.

The above evidence has been noted and considered. However, the instant specification is not enabled for the present broadly claimed invention for the reasons discussed below

The claims encompass a method of obtaining a GBV-B replicon enhaced cell, the method comprising curing cells of replicons (i.e., completley eliminating the GBV-B replicons), wherein curing could take place both *in vitro* and *in vivo* and wherein *in* vivo encompasses any animal species. While the art teaches that such a method can be performed *in vitro*, neither the art not the specification teach that such a method can be used for obtaining an enhanced cell *in vivo*. It is also noted that both the art and the specification teach that GBV-B does not infect animals other than new world monkeys. However, although the specification and the art teach that new world monkeys can be infected by GBV-B, the specification and the art do not provide any guidance as to practicing the claimed method in new world monkeys, since neither the specification nor the art do teach that IFN-$\alpha$ is able to cure the cells *in vivo* (i.e., to completely eliminate the replicon), as required by the claims. Along these lines, Aurisicchio et al. (J Virol, 2005, 79: 6772-6780) teach:

> "More importantly, tIFN efficiently inhibited GBV-B replicon in a Huh-7 hepatoma cell line at low HD-TET-tIFN doses. A certain degree of transcriptional control of tIFN was achieved in tamarins injected with HD-TET-iIFN, but under conditions used in this study, infection and replication of GBV-B was only delayed and not totally abrogated upon virus challenge."

Therefore, one of skill in the art would readily recognize that such a method cannot be applied *in vivo* to any animal. In conclusion, the specification provides enablement only for method of *in vitro* making a GBV-B replicon enhanced cell.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 2, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Lohmann et al. (Science, 1999, 285: 110-113, Applicant's IDS) or Blight et al. (Science, 2000, 290: 1972-1974, Applicant's IDS), in view of each Lanford et al. (J Virol, 2001, 75: 8074-8081), Khromykh et al. (J Virol, 1997, 71: 1497-1505) and Hong et al. (PGPUB 2001/0034019, of record).

Lohmann and Blight both teach a subgenomic HCV replicon with a deletion in the region of the genome encoding structural components, the subgenomic replicon comprising the HCV 5'-UTR, a neomycin phosphodiesterase gene (*neo*) as a selection sequence, the ECMV internal ribosome entry site (IRES), a NS3-NS5B sequence comprising functionally coupled to the EMCV IRES and an AUG initiation codon, and an HCV 3'-UTR, wherein the HCV replicon is capable of replication in Huh-7 cells (claim 1), wherein the HCV replicon further comprises an HCV structural region functionally coupled to the HCV 5'-UTR (claim 2), wherein the replicon is part of an expression vector comprising a promoter functionally coupled to the replicon nucleotide sequence (claim 12), and wherein the expression vector comprising the replicon is used in a process of making the replicon, wherein the process of making comprises transfecting cells with the expression vector and isolating the replicon (claim 13) (see Lohmann et

al., Abstract, p. 110, columns 2 and 3, p. 111, columns 1 and 2, Fig 1, p. 112, column 3, p. 113, column 2; Blight et al., p. 1972, column 2, p. 1973, Fig. 1). Neither Lohmann et al. nor Blight et al. teach a subgenomic GBV-B replicon (claims 1, 2, 12, and 13). However, the prior art teaches the advantage of obtaining similar subgenomic replicons with deletions in the genomic region encoding structural proteins for a variety of positive strand viruses. For example, Khromykh et al. teach the existence of subgenomic replicons for Sindbis virus, Semliki Forest virus, poliovirus, and human rhinovirus 14 and obtaining such a subgenomic replicon for the Kunjin virus (p. 1497, columns 1 and 2). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to use the teachings of Lohmann et al. and Blight et al. to obtain a similar subgenomic replicon for the GBV-B, with a reasonable expectation of success. By applying the above teachings, one of skill in the art would have necessarily obtained a subgenomic GBV-B replicon comprising the 5' and 3'-UTR of GBV-B (i.e., substantially similar to bases 1-445 of SEQ ID NO: 1 and the 3'-UTR consisting of bases 7710-8069 of SEQ ID NO: 1 respectiverly), and also an NS3-NS5b sequence substantially similar to bases 1938-7709 of SEQ ID NO: 1, as recited in claim 1 (compare Fig. 1 of Lohmann et al. and Fig. 1 of Blight et al. with Fig.4 of the instant application; see Hong et al., p. 1, paragraphs 0002 and 0010, and sequence alignments). The motivation to obtain such a subgenomic replicon is provided by Khromykh et al., who teach that such subgenomic replicons offer several advantages, such as deciphering the viral replication process, since such a subgenomic allows the separation of virion replication from virion assembly and maturation, a wide host range, a high level of cytoplasmic expression, and rapid

construction of recombinant replicons (p. 1497, columns 1 and 2). The motivation to apply the teachings of Lohmann et al. to GBV-B is provided by Lanford et al., who teach that GBV-B is suited to be used as a model for HCV antiviral studies (Abstract, p. 8074, column 2, p. 8075, column 1, first full paragraph, p. 8080, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such because the art teaches that GBV-B is the closest relative of HCV based on sequence homology, genome organization, and liver tropism. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

9. Claims 1, 2, 12, 13, 24, and 27 are rejected.

Claims 3-5 and 8-11 are free of prior art because the art does not teach a GBV-B replicon having a structural region comprising a sequence substantially similar to bases 446-487 of SEQ ID NO: 1, nor does the art provide motivation to use this particular sequence in constructing the replicon. Claim 7 is free of prior art because SEQ ID NO: 1 is not taught by the art. Claim 14 is free of prior art because the art does not provide any motivation to transfect GBV-B replicons into Huh-7 or Hep3B cells; the art teaches that GBV-B is not capable of infecting these cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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